A case of severe eosinophilic asthma and refractory rheumatoid arthritis well controlled by combination of IL-5Rα antibody and TNFα inhibitor

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journal or publication title	Allergology international
volume	68
number	4
page range	536-538
year	2019-10
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URL	http://hdl.handle.net/2241/00159730

doi: 10.1016/j.alit.2019.04.003

Allergology International 68 (2019) 536–538

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Letter to the Editor

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Dear Editor,

Benralizumab (Fasenra®) is a humanized, IL-5Rα-directed monoclonal antibody that induces rapid and nearly complete depletion of eosinophils, the dominating effector cells associated with asthma. The inhibition of eosinophilic inflammation or eosinophilia is expected to decrease airway injury, mucus hypersecretion, and bronchial hyperresponsiveness.[1,2] Golimumab (Simponi®) is a fully humanized monoclonal antibody against TNF -alpha (TNFα) that is administered once a month by subcutaneous injection. In Japan, golimumab is approved as monotherapy and/or in combination with methotrexate for the treatment of inflammatory arthritis, including rheumatoid arthritis (RA), in adults. Although strong evidence exists for the efficacy of these two therapeutic monoclonal antibodies against these respective diseases, almost no studies have been published on patients with these diseases who were treated with the two biologics simultaneously. Although treatment with a systemic steroid suppresses the activity of both diseases, it is also associated with many complications. In general, use of redundant immunosuppressive agents increases the severity of associated complications (especially infectious diseases). In contrast, most modern biologics act on specific factors or mediators that are critical for the targeted disease or disorder, and therefore, they are associated with fewer adverse effects than are systemic steroids. We here report on a case of combined severe eosinophilic asthma and refractory RA in which two biologics were simultaneously used to achieve control of both diseases.

A 69-year-old man was referred to our hospital by his primary physician. He had been diagnosed with allergic and eosinophilic asthma and RA in his 40s. He gave us written informed consent for publication of this case report. He was a previous smoker of 10–15 cigarettes a day for 18 years. He had no diagnosis of eosinophilic granulomatosis with polyangiitis. The diagnosis of RA was initially made on the basis of the presence of polyarthritis associated with autoantibodies such as rheumatoid factor (RF) and anticylic citrullinated peptide antibodies (anti-CCP) and on the basis of increased levels of CRP. At the time of diagnosis, his RA was stage 1; classification of the global functional status of his RA was class 3; and prednisolone, bucillamine, and salazosulfapyridine (SASP) were started. The laboratory findings at the initial visit to our hospital were as follows: white blood cell count, 6700/μl (eosinophils, 5.4% or 361/μl, max 600/μl); FeNO, 51 ppb; total IgE, 582 IU/ml; and specific IgE positive for house dust, mite, and cedar pollen. His forced vital capacity (FVC) was 72.2% of the predicted value; FEV_1, 49.8% of the predicted value; and FEV_1/FVC ratio, 55.95%. According to the score-based algorithm of the 2010 ACR/EULAR classification criteria for RA, his total score for the 4 categories was 8/10. His finger X-ray images taken at our hospital are shown in the Supplementary Figure 1. His asthma had been treated with inhalation therapy of ICS, LABA, and long acting muscarinic antagonist (LAMA). Just before visiting our hospital, when he was taking 7.5 mg of prednisolone every day, his CRP had gradually increased to 5 mg/dl and his joint symptoms had deteriorated. We started golimumab, which resulted in a rapid improvement in the joint pain, and the systemic steroids were discontinued. Then, as a nighttime asthmatic attack started to occur, we had to frequently use short courses of systemic steroids. After stopping the golimumab, we administered omalizumab, which was not effective. Then, he responded well to benralizumab, with his asthma symptoms improving remarkably, and the use of systemic steroids was discontinued. However, after 2 courses of benralizumab and the complete discontinuation of the systemic steroids, a worsening of his RA was observed. We stopped the benralizumab at this time, but the asthma quickly worsened. Given that both diseases were well controlled by use of the respective biologic agents, we decided to start the concomitant use of therapeutic monoclonal antibodies. Currently, 4 months have passed since the start of the combination therapy, and both diseases are well controlled without any prominent adverse effects. There is no need to consider short induction therapy with systemic steroids. After 3 courses of benralizumab, the %FEV_1 was 80% and the FeNO was 31 ppb. The asthma control test (ACT) had also improved to 22 from 19 (Fig. 1).

Asthma is traditionally regarded as a chronic airway disease, and recent studies have proven its heterogeneity on the basis of distinctive clusters or phenotypes of asthma. A recent retrospective population-based case–control study showed that patients with asthma had a significantly higher risk of developing RA than did healthy individuals,[3] suggesting the presence of a specific phenotype of severe asthma associated with RA.

In addition to IL-5, TNF-α is a proinflammatory cytokine that has been implicated in many aspects of the airway pathology of asthma.

Peer review under responsibility of Japanese Society of Allergology.

https://doi.org/10.1016/j.alit.2019.04.003

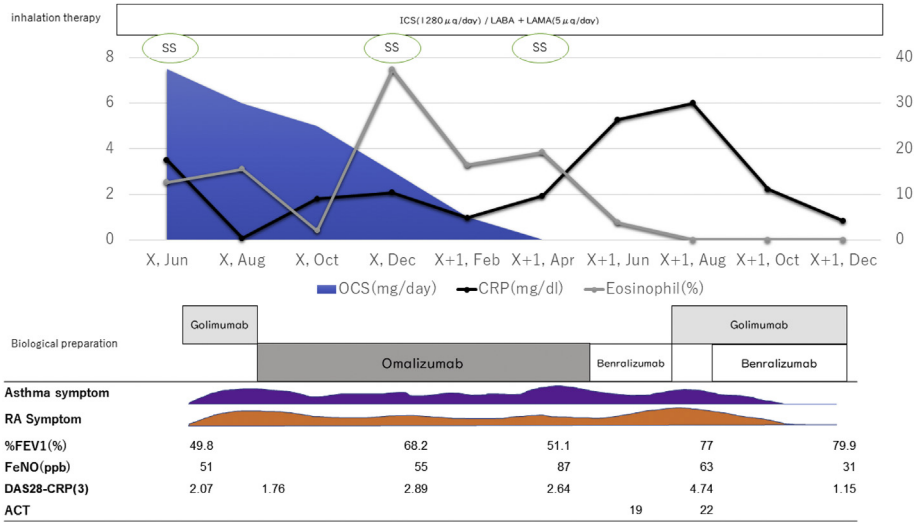

Fig. 1. Progress from visit to our hospital. SS, Additional administration of short courses of systemic steroids for treating acute asthma attacks; DAS 28-CRP(3), Disease Activity Score 3 variables (swollen joint, pain joint, CRP); ACT, Asthma Control Test. Left axis: Oral corticosteroids (OCS) (mg/day), CRP (mg/dl); Right axis: Eos (%).

It has been suggested that TNF-α delays human eosinophil apoptosis via TNF-receptor 1, resulting in changes in the longevity of human eosinophils.[4] The effects of golimumab on severe asthma have been the subject of several previous studies.[5,6] Some of those studies demonstrated an improvement in asthma quality of life, lung function, and airway hyperresponsiveness and a reduction in exacerbation frequency in patients treated with anti–TNF-α therapy. However, there was marked heterogeneity in the response, suggesting that these benefits are likely reserved to a small subgroup.[7,8]

Conversely, patients with RA had a 5-fold increase in serum ECP values as compared with healthy individuals. High serum ECP levels were particularly observed in patients with a disease of rather short duration but with a more aggressive course.[9] Furthermore, the treatment response of RA patients with mild eosinophilia at diagnosis could be worse than that of those without.[10]

Given the possibility that a synergistic effect may have been produced by combining anti-IL-5Rα and anti–TNF-α therapies, this case report could have important implications for asthma patients with the specific phenotype associated with RA, potentially enabling earlier disease recognition and opening the door to improved treatments including combination therapy using different biologic agents. Although, in this case, the possibility remains that the biologic agent for RA itself induced exacerbation of the asthma and vice versa, biologic combination therapies are expected to be used in the future and their efficacy will be assessed in larger studies.

Acknowledgments

We thank Ms F. Miyamasu, Medical English Communications Center, University of Tsukuba, for grammatical revision of the paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.alit.2019.04.003.

Conflict of interest

HY has received lecture fees from AstraZeneca and Boehringer Ingelheim. NHiz. has received lecture fees from AstraZeneca, Astellas Pharma, and Boehringer Ingelheim. The rest of the authors have no conflict of interest.

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Received 7 January 2019
Received in revised form 3 March 2019
Accepted 21 March 2019
Available online 24 April 2019